

# SMART syndrome: a late-onset and not always reversible complication of radiotherapy

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## SUMMARY

Stroke-like migraine attacks after radiation (SMART) syndrome is a rare and late complication of cerebral radiotherapy of unknown pathophysiology. It is characterised by hemicranial headache associated with persistent unilateral focal neurological signs and, occasionally, epileptic seizures. An increase in the frequency of SMART syndrome can be attributed to an increase in the survival rate of patients undergoing radiation therapy. This study details the case of a 60-year-old woman with a history of small-cell lung carcinoma, who, in her late forties, was treated with prophylactic cranial irradiation. She presented at the emergency room with acute onset of global aphasia, lethargy and headache that started a few days before.

## BACKGROUND

Stroke-like migraine attacks after radiation (SMART) syndrome is a delayed complication of brain irradiation characterised by recurrent neurological symptoms with episodes of complicated migraine symptoms and neurological deficits, including aphasia, hemiparesis and sensory disturbances and seizures.<sup>1,2</sup> SMART syndrome's pathogenesis is still unknown; the vast majority of cases described in the extant literature suggest a transient syndrome, with full recovery.

The clinical case discussed herein, however, is, to the best of our knowledge, unique. No treatment proved effective; nor did the patient's condition improve over time—in fact, quite the opposite occurred. These factors combined to make this case a significant diagnostic and therapeutic challenge.

## CASE PRESENTATION

A 60-year-old woman with hypertension, dyslipidaemia, hypothyroidism (secondary to Hashimoto thyroiditis), and a history of small cell lung carcinoma was admitted in April 2017 to the emergency room (ER) with acute onset of global aphasia, lethargy and a left hemicranial headache. The patient's small cell lung carcinoma was successfully treated in 2005 with chemotherapy, local radiotherapy and prophylactic cranial irradiation (50 Gy). At the time of her admission, the patient was in remission.

When the patient first arrived at the ER, she was afebrile with normal blood pressure. During the neurological examination, she was alert but exhibited impaired attention and global aphasia. She had no meningeal signs. Cerebral tomography (CT) revealed ischaemic/radiation leucoencephalopathy with no acute lesions. The cerebrospinal fluid analysis (including cytology) and laboratory studies

were unremarkable. The following day, the patient underwent an electroencephalogram (EEG) that showed left temporoparietal cortical dysfunction, without evidence of epileptiform activity. A second CT scan with contrast was performed, with similar results to those obtained at admission. The patient was given intravenous levetiracetam (LVT) (1 g two times a day), but showed no sign of improvement. Seventy-two hours after admission, the patient exhibited left gaze deviation, right homonymous hemianopsia, right central facial paralysis and right hemiparesis, and global aphasia. A cerebral magnetic resonance was performed, revealing no evidence of stroke or abnormal enhancement on postcontrast sequences. However, an abnormal signal in the left parieto-occipital cortical in the T2 fluid-attenuated inversion recovery (FLAIR) sequence ([figure 1](#)) was observed.

The patient was in her usual state of health prior to admission. Her family members confirmed that she had not recently experienced any infection, trauma, neck stiffness or seizure. However, they did report a number of headaches during the week prior to admission. There was no history of travel. Six days after admission, the patient experienced a generalised tonic-clonic seizure. Antiepileptic treatment was augmented to 1.5 g of LVT intravenous two times per day, after which the patient had no further tonic-clonic seizures. The patient's global aphasia and right hemiparesis, predominantly brachyfacial, persisted.

Further laboratory studies were requested. These revealed that the patient's antithyroid and anti-Peroxidase antibodies were positive. Seven days after admission, the patient started a 5-day regimen of methylprednisolone 1 g EV for the hypothesis of autoimmune disease and the possible diagnosis of SMART syndrome.

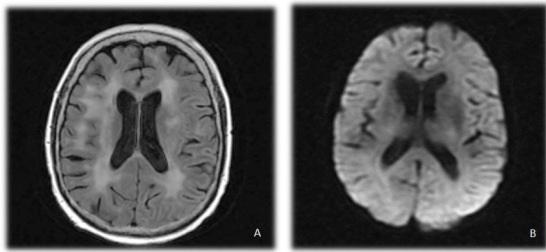
The patient continued to experience partial clonic seizures, necessitating a transfer to the intermediate care unit for more surveillance. Sodium valproate (VPA) 400 mg, three times a day, was added to her treatment. The corticotherapy and antiepileptic drugs had no effect on the patient, oscillating the degree of consciousness and maintaining partial seizures. Repeated lumbar puncture was normal (including oligoclonal bands, JC virus, serology for borrelia and herpes simplex, onconeural antibodies negative) except for weakly positive 14-3-3 protein.

Fifteen days after admission, the patient showed no sign of improvement. The diagnosis of autoimmune disease or paraneoplastic was considered, and the patient started immunoglobulins intravenous 2 g/kg for 5 days. Parathormone was added in a dose



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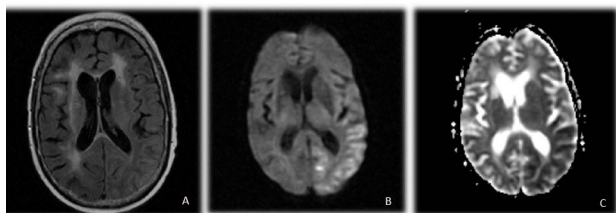
**Figure 1** Brain MRI with no abnormal enhancement on postcontrast sequences but with abnormal signal in the left parieto-occipital cortical in T2 FLAIR sequence (A). No restriction on diffusion-weighted imaging (B) and no contrast enhancement. FLAIR, fluid-attenuated inversion recovery.

of 100 mg three times daily. None of these treatments elicited a response. The patient's level of consciousness continued to decrease (Glasgow Coma Scale (GCS) of 7). Phenytoine (PHT) 100 mg three times a day was added to the existing antiepileptic regimen (LVT 1000+1000+1000, PHT 100+100+100, VPA 1000+1000+1000) without change. Brain angiography was not performed due to logistic questions. Over the course of the next 2 days, the patient's consciousness level improved slightly (GCS of 8) and no seizures were recorded. A decision was made to progressively reduce VPA, but 48 hours later, the patient developed partial myoclonic seizures with probable focal status epilepticus. Twenty-five days after admission to the ER, the patient was transferred to the intensive medicine care unit (IMCU) for the induction of burst-suppression pattern on EEG. A brain MRI was performed on the same day showing no abnormal enhancement on postcontrast sequences. The abnormal signal in the left temporoparietal cortical in T2 FLAIR sequence remained, and was now accompanied by restriction on diffusion-weighted imaging in the same area (figure 2). In total, the patient underwent six EEGs; not one of which provided evidence of epileptiform activity. After ceasing sedation in the IMCU, the patient's consciousness level started to increase. For the first time since admission, the patient was capable of social interaction.

#### OUTCOME AND FOLLOW-UP

Thirty days after admission, the patient left the IMCU. One month after stopping sedation and the reduction of antiepileptics, the patient demonstrated a positive clinical and radiological evolution, with an improvement in consciousness levels, aphasia and focal defects, and was discharged to a rehabilitation centre.

Five months after discharge, a follow-up revealed that the patient had almost completely recovered, with mild motor



**Figure 2** Brain MRI with no abnormal enhancement on postcontrast sequences but with abnormal signal in the left temporoparietal cortical in T2 FLAIR sequence (A) and restriction on diffusion-weighted imaging (B) and ADC sequence (C) in the same area. FLAIR, fluid-attenuated inversion recovery. ADC, apparent diffusion coefficient.

aphasia and mild difficulties walking being the only persistent symptoms.

#### DISCUSSION

The case described herein presented a novel diagnostic and therapeutic challenge, the results of which are consistent with the diagnosis of 'SMART' syndrome.

SMART syndrome is a late-onset complication of brain irradiation characterised by recurrent neurological symptoms coincident with episodes of complicated migraine symptoms and neurological deficits, including aphasia, hemiparesis, sensory disturbances and seizures.<sup>1 2</sup> Symptoms persist for a variable amount of time (hours to several weeks).

The pathogenesis of SMART is poorly understood. With its diverse clinical and radiographic features, the underlying mechanisms of SMART may be multifactorial.<sup>3</sup> Radiation is a likely cause as it is evident in all reported cases of the SMART syndrome.<sup>4</sup> Since it was first described in 1995, limited cases of SMART have been reported. The overall incidence is unknown.<sup>3</sup>

For many years, SMART syndrome was described as a reversible neurological dysfunction, however, it is now known that neurological impairment may be permanent.<sup>5</sup>

Imaging plays a crucial role in the diagnostic process; MRI findings show a high degree of similarity among affected individuals.<sup>3</sup> The hallmark features are reversible, transient, unilateral hyperintense cortical signal on T2-weighted and FLAIR sequences with gyriform enhancement, as well as a correlative abnormal T2 and FLAIR signal that disappears as symptoms resolve.<sup>3</sup>

Seizures are also frequently reported with SMART syndrome. Several studies suggested that ictal episodes of SMART syndrome are reversible.<sup>6</sup> Bompairé *et al* argue, however, that it is often impossible to formally identify seizure activity, and that anticonvulsant drugs are ineffective.<sup>7</sup> SMART syndrome may show a non-specific diffuse slowing pattern on the EEG. According to Zheng *et al*, seizures do not explain the clinical and radiological features of this syndrome and most cases failed to show epileptiform discharge. However, epileptiform activity during clinical seizures should not be regarded as inconsistent with a diagnosis of SMART. In our patient, the induction of a burst-suppression pattern on EEG was essential for recovery.

Some complementary investigations are recommended in order to establish a diagnosis of SMART syndrome. A gadolinium-enhanced MRI scan of the head is required. CSF examination, EEG, Magnetic Resonance Angiography (MRA), serum lactic acid level and blood pressure monitoring should also be considered.<sup>1</sup>

The most common complications of brain radiation include focal necrosis, progressive leukoencephalopathy and progressive decline in cognitive and neurological function.<sup>3</sup> The differential diagnosis from other complications of cerebral radiotherapy with contrast enhancement requires careful analysis of the clinical presentation. The diagnoses to exclude are peri-ictal pseudo-progression (in glioma patients), acute late-onset encephalopathy after radiotherapy and focal radionecrosis, acute infarction, posterior reversible encephalopathy syndrome, viral encephalitis, hemiplegic migraine, mitochondrial disorders, for example, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, and other metabolic conditions, for example, urea cycle disorders, postseizure cortical swelling and hemiplegic migraine.<sup>5 7 8</sup> All of these diagnoses were excluded in our patient.

SMART syndrome is a diagnosis of exclusion. Continued surveillance for other causes remains important.

The current literature suggests that in approximately 83% of patients, the natural course of SMART syndrome leads to a complete recovery.<sup>8</sup> However, Black *et al* reported an incomplete neurological recovery in 5 of their 11 patients, with permanent imaging sequelae (cortical laminar necrosis) developing as early as 17 days after the onset of symptoms in 27% of patients, suggesting that recovery can be partial or complete.<sup>2</sup>

There is no clear consensus regarding effective treatment for SMART.<sup>9</sup> Corticosteroids, antiplatelet agents, propranolol and verapamil have all been used without clear benefit.<sup>5,7</sup> According to a review by Di Stefano *et al*, steroids are frequently administered on empirical grounds, as they are thought to accelerate recovery.<sup>10</sup> Rapid control of seizure activity, if present, is important in treating patients with SMART syndrome.<sup>2</sup>

While the usual (or early stage) form of SMART syndrome improves spontaneously, even in cases with dramatic deficits, such as impaired level of consciousness, there is no effective treatment for the more severe form.<sup>7</sup>

SMART is a rare and late-onset complication of brain irradiation. Since 1995, this condition has attracted the attention of

many clinicians and neuroradiologists, leading to an increasing number of case reports and case series.<sup>3</sup> The improvements in cancer survival rates have resulted in a rise in its frequency. SMART syndrome appears to be a specific clinical syndrome with a course that can progress from a benign reversible form to a severe and irreversible form.<sup>7</sup> Awareness of this syndrome is diagnostically important and can obviate unnecessary invasive investigations such as brain biopsy or cerebral angiography.

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## REFERENCES

- Black DF, Bartleson JD, Bell ML, *et al*. Smart: stroke-like migraine attacks after radiation therapy. *Cephalalgia* 2006;26:1137–42.
- Black DF, Morris JM, Lindell EP, *et al*. Stroke-Like Migraine Attacks after Radiation Therapy (SMART) Syndrome Is Not Always Completely Reversible : A Case Series 2013:2298–303.
- Zheng Q, Yang L, Tan L-M, *et al*. Stroke-Like migraine attacks after radiation therapy syndrome. *Chin Med J* 2015;128:2097–101.
- Singh AK, Tantiwongkosi B, Moise A-M, *et al*. Stroke-Like migraine attacks after radiation therapy syndrome: case report and review of the literature. *Neuroradiol J* 2017;30:568–73.
- Lim SY, Brooke J, Dineen R, *et al*. Stroke-Like migraine attack after cranial radiation therapy: the smart syndrome. *Pract Neurol* 2016;16:406–8.
- Pruitt A, Dalmau J, Detre J, *et al*. Episodic neurologic dysfunction with migraine and reversible imaging findings after radiation. *Neurology* 2006;67:676–8.
- Bompaire F, Zinchenko L, Lahutte M, *et al*. Smart syndrome: classic transient symptoms leading to an unusual unfavorable outcome. *Rev Neurol (Paris) [Internet]* 2016;1–7 <http://linkinghub.elsevier.com/retrieve/pii/S0035378716300765%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/27919464>
- Rigamonti A, Lauria G, Mantero V, *et al*. Smart (stroke-like migraine attack after radiation therapy) syndrome: a case report with review of the literature. *Neurol Sci* 2016;37:157–61.
- Tomek M, Bhavsar SV, Patry D, *et al*. The syndrome of stroke-like migraine attacks after radiation therapy associated with prolonged unresponsiveness in an adult patient. *Neurologist* 2015;19:49–52 <http://www.ncbi.nlm.nih.gov/pubmed/25607333>
- Di Stefano AL, Berzero G, Ducray F, *et al*. Stroke-Like events after brain radiotherapy: a large series with long-term follow-up. *Eur J Neurol* 2019;26:639–50.

## Learning points

- ▶ Stroke-like migraine attacks after radiation (SMART) syndrome is a rare, late-onset complication of brain irradiation. Increased cancer survival rate have resulted in an increase in its frequency.
- ▶ The diagnosis of SMART syndrome should be considered whenever gyriform enhancement is noted in the parieto-occipital region in a patient with migraine-type headaches, seizures and stroke-like symptoms with a remote history of brain radiation.
- ▶ Awareness of this syndrome is important to make a proper diagnosis and avoid unnecessary interventions or therapies. There are no specific treatments for SMART syndrome.
- ▶ Despite the uncertain benefit of the current treatment options, it is important to obtain a rapid control of seizure activity. Steroids are frequently administered on empirical grounds, as they are thought to accelerate recovery.
- ▶ The prognosis is mostly favourable. The recognition of this syndrome will avoid unnecessary invasive investigations.

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